Routine follow-up intervals in patients with high-grade squamous intraepithelial lesions (HSIL) and free excision margins can safely be increased in the first two years after Large Loop Excision of the Transformation Zone (LLETZ)

Eijsink, J. J. H.; de Bock, G. H.; Kuiper, J. L.; Reesink-Peters, N.; van Hemel, B. M.; Hollema, H.; Nijman, H. W.; Mourits, M. J. E.; van der Zee, A. G. J.

Published in:
Gynecologic Oncology

DOI:
10.1016/j.ygyno.2008.11.022

Publication date:
2009

Gynecologic Oncology 113 (2009) 348–351

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Routine follow-up intervals in patients with high-grade squamous intraepithelial lesions (HSIL) and free excision margins can safely be increased in the first two years after Large Loop Excision of the Transformation Zone (LLETZ)

J.J.H. Eijsink [a], G.H. de Bock [b], J.L. Kuiper [a], N. Reesink-Peters [a], B.M. van Hemel [c], H. Hollema [c], H.W. Nijman [a], M.J.E. Mourits [a], A.G.J. van der Zee [a,*]

[a] Department of Gynecologic Oncology, University Medical Center Groningen, University of Groningen, PO Box 30001 9700 RB Groningen, The Netherlands
[b] Department of Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands
[c] Department of Pathology, University Medical Center Groningen, University of Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 29 September 2008
Available online 17 March 2009

Keywords:
High-grade squamous intraepithelial lesion (HSIL)
Large Loop Excision of the Transformation Zone (LLETZ)
Excision margin
Follow-up
Protocol
Compliance

ABSTRACT

Objective. To assess the compliance of HSIL patients to the national Dutch routine follow-up protocol in the first 2 years after LLETZ and to determine if based on the status of excision margins, follow-up intervals could be modified.

Methods. A prospective cohort study was performed in patients, referred because of an abnormal Pap smear between 1996 and 2004 and treated for HSIL with LLETZ. The Dutch national routine follow-up protocol orders a Pap smear after 6, 12 and 24 months, respectively. Follow-up results were completed by using PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands. To assess compliance to the follow-up protocol, adequate follow-up was defined as three cervical smears taken after 6 (+/−3), 12 (+/−3) and 24 (+/−3) months, respectively.

Results. Compliance to the first 2 years follow-up protocol declined from 86.2% to 64.8% to 51.2% for first, second and third follow-up cervical smears, respectively. Patients with involved excision margins had a three times higher overall risk of developing a subsequent HSIL after LLETZ as compared to patients with free excision margins (HR: 3.2, 95% CI = 1.3–7.9, $p = 0.01$). Risk for diagnosing HSIL during the first 12 months of follow-up for patients with free excision margins was only 1%.

Conclusions. Compliance to the Dutch national routine follow-up protocol in HSIL patients after LLETZ is only moderate. For HSIL patients with free excision margins after LLETZ the first cytological follow-up interval can safely be increased to 12 months.

Introduction

Cytological examination of the cervix enables identification of asymptomatic precursor lesions of cervical cancer, so-called squamous intraepithelial lesions (SILs). Widespread introduction of population-based screening programs for these precursor lesions in developed countries contributed to a lower mortality and morbidity rate for cervical cancer. However, especially due to absence of population-based screening programs in many low-income countries the incidence of cervical cancer in 2002 was still 493,000 cases with a mortality rate of 273,000 women worldwide in 2002 [1].

Progression to cervical cancer of pre-malignant lesions is estimated to be 1% for low-grade SILs (LSILs) and up to 50% for high-grade SILs (HSILs) [2,3]. Therefore, many clinicians feel compelled to treat patients with HSILs, while patients with LSILs are often followed up. Different techniques have been developed for treatment of HSILs and these are all equally effective [4–6]. Nowadays treatment of choice for HSILs is a Large Loop Excision of the Transformation Zone (LLETZ). Advantages of this method are the simplicity of the procedure and the production of a specimen for histological diagnosis, thereby allowing assessment of the excision margins [7]. Using therapy in an outpatient setting to treat HSIL reduces the risk of cervical cancer by 95% in the first 8 years after therapy [8]. However, the risk of cervical cancer, even with a careful long-term follow-up scheme, remains five times greater for these patients as compared to the general population [9]. For that reason, after initial treatment with LLETZ patients usually are followed up at different intervals by cervical smear and/or colposcopy for early detection of a subsequent SIL. Many different protocols at different intervals for follow-up after LLETZ have been used and to our knowledge no data are available on compliance. After incomplete

* Corresponding author. Fax: +31 50 3611806.
E-mail address: a.g.j.van.der.zee@og.umcg.nl (A.G.J. van der Zee).

0090-8258/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2008.11.022

excision it is well known that the chance of developing a subsequent SIL is higher when compared to complete excision [10].

After treatment of HSIL, the current Dutch national guideline for follow-up includes a cervical smear at 6, 12 and 24 months after LLETZ. In case of no subsequent SIL during this 24 months follow-up, patients will return to the population-based screening program (one cervical smear every 5 years for women between 30–60 years), performed by general practitioners. Aims of the present study were to assess the compliance of our HSIL patients to the national Dutch routine follow-up protocol in the first 2 years after LLETZ and to determine if, based on the status of excision margins, follow-up intervals in the first 2 years could be modified.

Patients and methods

Patients

A prospective cohort study was performed in patients who were referred because of an abnormal Pap smear to the outpatient clinic of the Department of Obstetrics and Gynecology of the University Medical Center Groningen (UMCG), The Netherlands between 1996 and 2004. During this time period, patients were asked to participate in various studies on new biomarkers in cervical neoplasia. In light of these studies information on data, diagnoses and treatment details were prospectively collected in separate databases after retrieval from the electronic patient files. For the present study only anonymised data from patients who had given written informed consent to participate in the previously mentioned studies, which were all approved by the Institutional Review Board (IRB) from the UMCG, were used.

Diagnostic work-up and treatment protocol

Patients with a Pap 2 (atypical cells) or Pap 3A (mild/moderate dysplasia) cervical smear first underwent colposcopy and biopsy. Histological diagnosis of HSIL after biopsy was followed by LLETZ. Patients referred to the outpatient clinic with a Pap 3B (severe dysplasia) cervical smear or higher, without suspicion of cervical cancer, underwent colposcopy and LLETZ in the same session. After LLETZ the routine follow-up of patients consists of a cervical smear at 6, 12 and 24 months, taken by a gynecologist at the outpatient clinic of the UMCG. In case of no subsequent SIL, patients returned to the population based screening program, which implies one cervical smear by the general practitioner every 5 years for women between 30 and 60 years. This protocol is in accordance with national Dutch guidelines for follow-up after LLETZ since 1996. In case of an abnormal cervical smear during follow-up the patient was scheduled for colposcopy and biopsy or re-LLETZ.

Histological examination of all specimens was performed by an experienced gynecologic pathologist (HH). Since 1996 the statuses of the endocervical and ectocervical excision margins of a LLETZ are examined systematically. Excision margins were labeled as positive when endocervical and/or ectocervical margins showed dysplasia.

Selection criteria

Between January 1996 and December 2004, 808 patients visited our outpatient clinic because of abnormal Pap smear. For the present study we selected 520 patients, who underwent LLETZ for HSIL, from the database. Median follow-up of the study population was 53 months with a minimum of 6 months and a maximum of 131 months.

Follow-up data collection

PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands, was used to complete follow-up information regarding the results of cervical smears during follow-up. For all patients, all cytological and histological follow-up information on date, kind of treatment and results were collected. Follow-up data were collected till March 2007.

Statistical analysis

For data collection and analysis, the software system of SPSS software package was used (SPSS 14.0, Chicago, IL, USA). To assess compliance to the follow-up protocol, we defined complete follow-up as cervical smears taken after 6 (+/−3), 12 (+/−3) and 24 (+/−3) months, respectively. Analysis for compliance to the follow-up protocol at the different time points in the first 2 years was only performed for those patients in whom a complete follow-up protocol was still possible, i.e. patients who did not have a second smear were censored for the analysis at the third time point. In addition, patients with an abnormal or not to judge Pap smear during follow-up and patients who underwent a hysterectomy for other reasons were censored. The time from the LLETZ to the incidence of SIL in follow-up was assessed for patients with free excision margins as compared to patients with margins not free of dysplasia, by using a Kaplan Meier model. Differences were tested by using a log-rank test. In addition, Cox regression analyses were performed to estimate the impact of excision margins on the incidence of SIL and HSIL. To estimate the overall probability of SIL occurring at different time points, life-tables were constructed. Statistical significance was assumed if the p value was <0.05.

Results

Any cytological follow-up was performed in 515/520 (99%) eligible HSIL patients who underwent LLETZ. Compliance to the follow-up protocol declined from 86.2% to 64.8% to 51.2% for first, second and third cervical smears, respectively (Table 1). Therefore, only 51.2% of the HSIL patients treated with LLETZ completed the total follow-up program in the first 2 years.

An abnormal Pap smear (Pap 2 >) during overall follow-up was found in 62/515 (12.0%) patients. Histological follow-up specimens were available from biopsies, LLETZ and hysterectomies (also for non-cervical neoplasia reasons) for 83/515 (16.1%) patients.

Table 1
Compliance to follow-up protocol.

Category	First cervical smear	Category	Second cervical smear	Category	Third cervical smear
Eligible	515		515		455
Censored[a]	0		60		72
<3 months	6 (1.2%)	<9 months	22 (4.8%)	<21 months	44 (11.5%)
3–9 months	444 (86.2%)	9–15 months	295 (64.8%)	21–27 months	196 (51.2%)
>9 months	65 (12.6%)	>15 months	138 (30.3%)	>27 months	143 (37.3%)
Total	515 (100%)	Total	455 (100%)	Total	383 (100%)

[a] Censored: patients after first and second follow-ups with no cervical smear, with an abnormal or not to judge cervical smear or a hysterectomy.

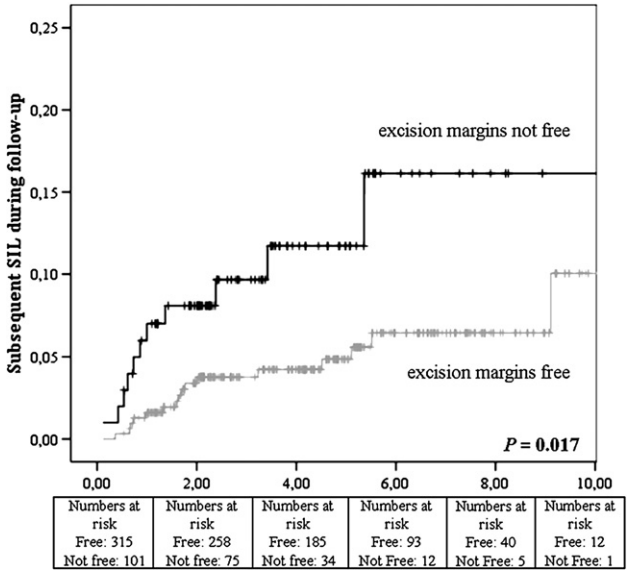

Fig. 1. Time (in years) to subsequent SIL (LSIL or >) based on the status of excision margins. Time to subsequent SIL (LSIL or >) was estimated by the Kaplan–Meier method and evaluated by log-rank test.

Histological diagnosis of these follow-up specimens was: 1 (0.2%) not available, 42 (8.2%) no dysplasia, 13 (2.5%) LSIL and 22 (4.2%) HSIL. In 35/515 (6.8%) patients subsequent SILs were diagnosed; 24/35 (68.6%) during the first 2 years of follow-up and 11/35 (31.4%) after 2 years follow-up. During the first 2 years of follow-up 12/22 (54.5%) HSILs were diagnosed and after 2 years 10/22 (45.5%). For patients with an abnormal Pap smear during follow-up ($n=62$), histological specimens were obtained from 41 (66%) patients. Histological diagnosis of these specimens was: 14 no dysplasia, 9 LSIL and 18 HSIL.

Excision margins were free of dysplasia in 315 (61.2%) patients, not free of dysplasia in 101 (19.6%) patients and difficult to determine or not mentioned in 99 (19.2%) patients. As a result 416 patients were available for the analysis of the association between excision margins and subsequent SIL. Fig. 1 shows the occurrence of subsequent SIL in relation to the status of the excision margins. In 315 patients with free excision margins 17 (5.4%) subsequent SILs were diagnosed as compared to 11 (10.9%) subsequent SILs in 101 patients with involved excision margins (log-rank test, $p=0.017$). Patients with involved excision margins therefore had more than two times higher chance of developing a subsequent SIL compared to patients with free excision margins (HR: 2.5, 95% CI = 1.1–5.3, $p=0.021$).

In patients with free excision margins and subsequent SILs ($n=17$), 6 patients were diagnosed with LSIL and 11 patients were diagnosed with HSIL. In patients with involved excision margins and subsequent SIL ($n=11$), 2 patients were diagnosed with LSIL and 9 patients were diagnosed with HSIL. In Fig. 2 subsequent HSIL for free excision margins, 3.5% (11/315), is compared with subsequent HSIL for involved excision margins, 8.9% (9/101) (log-rank test, $p=0.006$). Patients with involved excision margins had a three times higher chance of developing subsequent HSIL compared to patients with free excision margins (HR: 3.2, 95% CI = 1.3–7.9, $p=0.01$).

Table 2 shows in more detail the risk of detecting SIL during follow-up. The overall risk for HSIL was 0% after first 6 months, 2% after 1 year and 1% after 2 years. The overall risk for SIL was 1% after first 6 months, 3% after 1 year and 2% after 2 years. If we only consider patients with free excision margins, the overall risk for HSIL is even lower, 0% after 6 months, 1% after 1 year and 1% after 2 years. In patients with involved excision margins the overall risk is 2% after 6 months, 6% after 1 year and 1% after 2 years.

Discussion

Our study indicates that patients diagnosed with HSIL, treated with LLETZ and free excision margins have a negligible risk (1%) for detection of HSIL during the first 12 months of follow-up. Therefore, for HSIL patients after LLETZ with free excision margins the first follow-up visit might be postponed until 12 months after treatment.

Recently a meta-analysis by Ghaem-Maghami et al. showed a pooled prevalence of overall 22% post-treatment cervical dysplasia (defined as abnormal cytology or histology) for patients treated with loop diathermy and involved excision margins [10]. The lower prevalence of post treatment cervical dysplasia (6.8%) in our study compared to this meta-analysis is probably due to the definition of post-treatment disease, which was defined as histological proven LSIL or higher in our study. Another explanation could be that in our hospital management of patients with abnormal Pap smears is centralized at the Cervical Dysplasia Outpatient Clinic. All patients are treated by a small group of medical doctors, specialized in colposcopy and LLETZ, using a standardized treatment protocol over years. Ghaem-Maghami et al. recommended that patients with incomplete excision margins need close follow-up for at least 10 years and some patients may benefit from an immediate second treatment [10]. Several other studies suggested to follow-up patients with incomplete excision more intensively by colposcopy and/or cytology, because of an increased risk of subsequent dysplasia [11–14]. Our study however again illustrates that the far majority of patients with incomplete excision do not develop HSIL, so intensive follow-up will result in a possible benefit for only a very small number of these patients.

Persistent post-treatment high-risk human papillomavirus (hr-HPV) is a risk factor for subsequent SIL [15,16]. A meta-analysis of Zielinski et al. showed that the status of excision margins, post-treatment cytology, post-treatment hr-HPV or combinations had a negative predictive value of 91–99%, the positive predictive values of these parameters were 25–51% [17]. Based on this study they proposed to follow-up patients with negative cytology in combination with negative hr-HPV DNA testing less intensively. Still the need for a marker with a higher positive predictive value remains, which allows more individually modification of follow-up protocols.

The effectiveness of a follow-up protocol is limited by the compliance to the protocol by both medical doctor and patient. In our study compliance to the follow-up protocol in the first 2 years

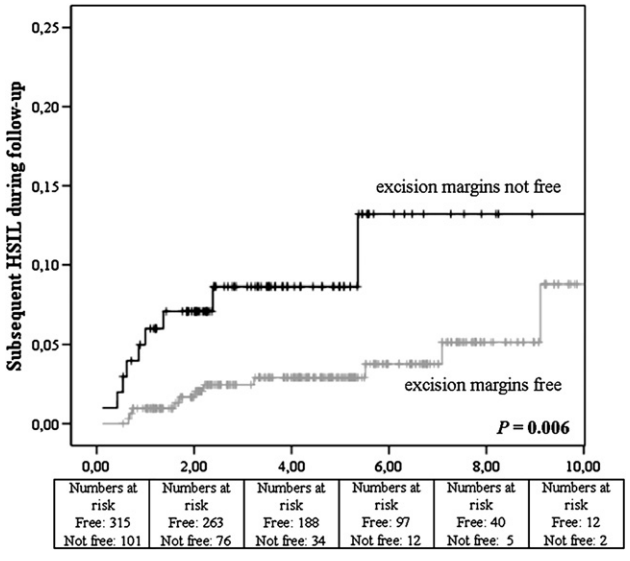

Fig. 2. Time (in years) to subsequent HSIL based on the status of excision margins. Time to subsequent HSIL was estimated by the Kaplan–Meier method and evaluated by log-rank test.

Table 2
Probability developing SIL over time.

	Probability SIL total group ($n=515$)		Probability SIL for excision margins ($n=416$)		Probability HSIL for excision margins ($n=416$)	
Time point	SIL	HSIL	Free	Not free	Free	Not free
6 months	1%	0%	0%	2%	0%	2%
12 months	3%	2%	2%	7%	1%	6%
24 months	2%	1%	2%	1%	1%	1%

after LLETZ was only 51%. To our knowledge there are no data on compliance to the follow-up protocol after LLETZ. An explanation for the moderate compliance that we observed could be that the simplicity of the LLETZ procedure in an outpatient setting, may give to patients the idea that their condition is less severe and therefore needs less follow-up care [18]. Another explanation might be that anxious women are less likely to attend for a repeat cervical smear within the recommended time frame [19]. If the last explanation is true, anxiety for follow-up visits should be decreased by face-to-face education and supportive care after colposcopy [20]. Although our follow-up was mainly performed by the same medical doctor who also performed the LLETZ, compliance was still disappointing. With the current decreasing compliance over time, it might be more effective to bypass the first follow-up visit after 6 months and focus on increasing compliance 1 year after LLETZ. Furthermore, the need for long-term follow-up should be emphasized, because due to the weak performance of the Pap smear [21] in combination with moderate compliance to the follow-up protocol and the fact that almost half of the subsequent HSILs (45.5%) are diagnosed after the first 2 years of the routine follow-up protocol, the risk of developing cervical cancer for HSIL patients after LLETZ is still present.

In conclusion, our study in a large, well documented series of patients indicates that compliance to the Dutch national routine follow-up protocol in HSIL patients after LLETZ is only moderate. For HSIL patients treated with LLETZ and free excision margins first follow-up interval might safely be increased to 12 months.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

References

[1] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55(2):74–108.
[2] Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol 1993;12(2):186–92.
[3] McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol 2008.
[4] Duggan BD, Felix JC, Muderspach LI, Gebhardt JA, Groshen S, Morrow CP, et al. Cold-knife conization versus conization by the loop electrosurgical excision procedure: a randomized, prospective study. Am J Obstet Gynecol 1999;180 (2 Pt 1):276–82.
[5] Martin-Hirsch PL, Paraskevaidis E, Kitchener H. Surgery for cervical intraepithelial neoplasia. Cochrane Database Syst Rev 2000(2):CD001318.
[6] Mitchell H, Hocking J. Influences on the risk of recurrent high grade cervical abnormality. Int J Gynecol Cancer 2002;12(6):728–34.
[7] Kyrgiou M, Tsoumpou I, Vrekoussis T, Martin-Hirsch P, Arbyn M, Prendiville W, et al. The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia: the Cochrane colposcopy and cervical cytopathology collaborative group (C5 group) approach. Cancer Treat Rev 2006;32(7):516–23.
[8] Soutter WP, Lopes AD, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. Lancet 1997;349(9057):978–80.
[9] Kalliala I, Anttila A, Pukkala E, Nieminen P. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. BMJ 2005;331(7526):1183–5.
[10] Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. Lancet Oncol 2007;8(11):985–93.
[11] Dobbs SP, Asmussen T, Nunns D, Hollingworth J, Brown LJR, Ireland D. Does histological incomplete excision of cervical intraepithelial neoplasia following large loop excision of transformation zone increase recurrence rates? A six year cytological follow up. Br J Obstet Gynaecol 2000;107(10):1298–301.
[12] Flannelly G, Bolger B, Fawzi H, Lopes AD, Monaghan JM. Follow up after LLETZ: could schedules be modified according to risk of recurrence? Br J Obstet Gynaecol 2001;108(10):1025–30.
[13] Gardeil F, Barry-Walsh C, Prendiville W, Clinch J, Turner MJ. Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. Obstet Gynecol 1997;89(3):419–22.
[14] Dietrich III CS, Yancey MK, Miyazawa K, Williams DL, Farley J. Risk factors for early cytologic abnormalities after loop electrosurgical excision procedure. Obstet Gynecol 2002;99(2):188–92.
[15] Acladious NN, Sutton C, Mandal D, Hopkins R, Zaklama M, Kitchener H. Persistent human papillomavirus infection and smoking increase risk of failure of treatment of cervical intraepithelial neoplasia (CIN). Int J cancer 2002;98(3):435–9.
[16] Paraskevaidis E, Koliopoulos G, Alamanos Y, Malamou-Mitsi V, Lolis ED, Kitchener HC. Human papillomavirus testing and the outcome of treatment for cervical intraepithelial neoplasia. Obstet Gynecol 2001;98(5 Pt 1):833–6.
[17] Zielinski GD, Bais AG, Helmerhorst TJ, Verheijen RHM, de Schipper FA, Snijders PJF, et al. HPV testing and monitoring of women after treatment of CIN 3: review of the literature and meta-analysis. Obstetrical & Gynecological Survey 2004;59(7): 543–53.
[18] Greenspan DL, Faubion M, Coonrod DV, Hart KW, Mathieson K. Compliance after loop electrosurgical excision procedure or cold knife cone biopsy. Obstet Gynecol 2007;110(3):675–80.
[19] French DP, Maissi E, Marteau TM. Psychological costs of inadequate cervical smear test results. Br J Cancer 2004;91(11):1887–92.
[20] Le T, Hopkins L, Menard C, Hicks-Boucher W, Lefebvre J, Fung Kee FM. Psychologic morbidities prior to loop electrosurgical excision procedure in the treatment of cervical intraepithelial neoplasia. Int J Gynecol Cancer 2006;16(3):1089–93.
[21] Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med 2000;132(10): 810–9.